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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/787,229	04/23/2001	Venkata-Rangarao Kanikanti	LEA 33 253	8002

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EXAMINER
SHEIKH, HUMERA N

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 08/22/2003

15

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/787,229	KANIKANTI ET AL.	
	Examiner	Art Unit	
	Humera N. Sheikh	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 June 2003 (paper no. 14)* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,12 and 13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,12 and 13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Application

Receipt of the request for an extension of time (3 months) and the Request for Continued Examination (RCE) under Rule 1.114, both filed 06/25/03 is acknowledged.

Claims 1-8, 12 and 13 are pending. Claims 1, 7 and 12 have been amended. New claim 13 has been added. Claims 1-8, 12 and 13 are rejected.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-8, 12 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jenkins *et al.* (EP 0 205 282 B1) or Jenkins *et al.* (US Pat. No. 4,940,587) in view of Arwidsson et al. (US Pat. No. 5,783,215).

Jenkins *et al.* (EP 0 205 282 B1 and US Pat. No. 4,940,587) teach a process for the preparation of a sustained release, oral pharmaceutical composition, comprising a hydrophilic polymer HPC -hydroxypropyl cellulose having an average molecular weight of greater than 200,000, especially above 500,000 in combination with a pharmaceutically active compound (i.e., nifedipine), wherein the active-compound polymer mixture is formed into coated granules having a particle size of less than 1000 micrometers, and preferably less than 100 microns for use in oral administration dosage forms (see EP reference pages 2-4 and examples and US reference columns 2-3 and examples).

Jenkins (US '587) at columns 3 and 4 teach a various array of drugs to be formulated with the hydrophilic polymer. Suitable active agents include analgesics, anti-inflammatory agents, antihistamines, vasodilators, hormones, etc. Particularly preferred drugs for use in the composition are morphine, nifedipine, phenazocine, verapamil and saltutamol (col. 3, line 7 thru col. 4, line 10).

Example 6, for instance, demonstrates the preparation of nifedipine tablets, whereby nifedipine (20 gm), xylitol, lactose, hydroxyethyl cellulose and hydroxypropyl cellulose (20 gm) were hydrated and thoroughly mixed until a granular mass was obtained. The hydrated material was partially dried in a fluid bed dryer, granulated and

sieved, to which a coating of hydroxypropyl cellulose was then added. The coated granules were then compressed into tablets (see paragraphs bridging cols. 6 and 7).

Regarding the molar degree of substitution, Jenkins does not explicitly disclose a molar degree of substitution of at least three. It is unclear whether Jenkins et al. teaches the different degrees of molar substitution being well above three. Assuming that these are different and in the absence of showing otherwise, it is deemed obvious to one of ordinary skill in the pharmaceutical art to obtain a suitable degree of molar substitution through routine or manipulative experimentation to obtain the best possible results according to the purpose intended.

Jenkins teaches that the concentration of the cellulose is preferably between 2% and 15% (page 3, lines 7-8) and does not explicitly teach the applicant's claimed range of 40-95%. One of ordinary skill familiar in the pharmaceutical art could, through the use of routine or manipulative experimentation determine suitable polymer ranges to obtain the best possible results, as these are viewed as variable parameters. Furthermore, Jenkins clearly teaches the same ingredients for a similar intended purpose and therefore the expected results would also be the same. The applicant's have not demonstrated any degree of criticality of the instant polymeric ranges.

As discussed above, Jenkins teaches a process for the preparation of a sustained release, oral pharmaceutical composition, comprising a hydrophilic polymer HPC -hydroxypropyl cellulose in combination with a pharmaceutically active compound. Jenkins teaches at column 5, lines 12-20 that the compressed granules may be formed into any suitable oral dosage form. Jenkins discloses the formation of tablets in his

examples. It would have been obvious to one of ordinary skill in the art to formulate pellets, granules or particles into any suitable dosage form, such as by compression for forming tablets or filling of particles or granules into capsules. Such skill is also evident from the reference of Arwidsson '215 (see below).

Arwidsson *et al.* teach an orally administered controlled release multiple unit dose preparation comprising an active substance (i.e., nifedipine) dispersed in or homogeneously mixed with a hydrophilic polymer, hydroxypropylcellulose wherein the formulation contains beads or multiple units that are capable of being and are favorably filled into capsules or sachets or compressed to form tablets. According to Arwidsson, multiple unit dosage systems that are filled into capsules or sachets, require sufficient mechanical properties to withstand processing. Arwidsson teaches that surprisingly, the addition of a hydrophilic polymer in a layer together with the active substance in specific amounts, gives favorable mechanical properties withstanding cracking, especially of the release controlling membrane, when exposed to mechanical stresses, e.g., during filling in capsules or sachets or during compaction (see reference column 1, line 12 thru col. 5, line 25).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the combined teachings of Arwidsson within either Jenkins (US '587) or Jenkins (EPO '282) because Arwidsson explicitly teaches a controlled release multiple unit dose preparation comprising an active substance (i.e.,

nifedipine) dispersed in or homogeneously mixed with a hydrophilic polymer (HPC), wherein the formulation contains beads or multiple units that are favorably filled into capsules or compressed into tablets and similarly the Jenkins references teach a combination of a hydrophilic polymer (HPC) in combination with an active substance (i.e., nifedipine) in any suitable dosage form, particularly tablets. The expected result would be an effective process for the formulation of an oral multiple-unit preparation, which advantageously can be formulated into tablets, capsules or sachets, as similarly desired by the applicants.

Response to Arguments

Applicant's arguments filed 06/25/03 have been fully considered but they are not persuasive. The applicant argued regarding the 35 U.S.C. 103(a) rejections for claims 1-8 and 12 by Jenkins (EP 0 205 282) or Jenkins (US Pat. No. 4,940,587).

The applicant argued, "The pharmaceutical compositions and processes described in Jenkins differ significantly in purpose and effect from those of the instant invention. Jenkins compositions contain an aliphatic alcohol, a hydroxyalkyl cellulose and a pharmaceutical. In contrast, the composition of the instant application contains only a granulated mixture of hydroxypropylcellulose and a pharmaceutical without the alcohol. Additionally, the granulated mixture of hydroxypropylcellulose and pharmaceutical is not coated, as required by Jenkins. Further the instant compositions

are not compressed. Additionally, the particles may be lacquered to prevent agglomeration. The difference between compressing the granules into a tablet, as described by Jenkins, and filling capsules or other suitable delivery vehicles with loose granules is the primary difference between the process of Jenkins and the instant application."

These arguments have been fully considered but were not found to be persuasive. The instant invention is drawn to a process for the production of an orally administrable multiple-unit sustained release pharmaceutical composition comprising the steps of: (a) combining hydroxypropylcellulose polymer (average molecular weight-250,000 to 1,200,000 and a molar degree of substitution of at least 3) in an amount from 40 to 95% by weight with a pharmaceutically acceptable compound to obtain a mixture of a compound; (b) converting said mixture into particles having a diameter of 0.2 to 3.0 mm; and (c) filling said particles into an orally administrable multi-unit sustained release dose form.

Jenkins teaches a process for the preparation of a sustained release, oral pharmaceutical composition, comprising a hydrophilic polymer HPC -hydroxypropyl cellulose having an average molecular weight of greater than 200,000, especially above 500,000 in combination with a pharmaceutically active compound. The granules have a particle size of less than 1000 micrometers and preferably less than 100 micrometers. Jenkins discloses that the concentration of the cellulose is preferably between 2% and 15%. Jenkins teaches the generic concept of including a hydrophilic polymer (HPC) having a high molecular weight in a sustained release oral formulation. Jenkins teaches

similar ranges or percentages as claimed. Furthermore, suitable ranges can be manipulatively altered to accommodate the intended purpose. In fact, generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. [W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. *In re Aller*, 220 F. 2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). The argument that Jenkins teaches additional ingredients (i.e., aliphatic alcohol, hydroxyalkyl cellulose) and teaches a coating whereas the instant application does not include such ingredients, nor a coating, was not found to be persuasive since the instant process claims are "comprising" claims and hence the utilization of the "comprising" claim language permits the exclusion or inclusion of additional ingredients. Such additional ingredients, since used in the art previously, would not be considered as being detrimental to the formulation itself. Jenkins teaches an *oral* pharmaceutical composition comprising a polymer with an active ingredient. Jenkins teaches an orally administrable pharmaceutical composition comprising the same ingredients, in similar amounts with a similar intended purpose as the applicant. Jenkins teaches that any suitable dosage form may be used, particularly tablets. Jenkins does not teach filling particles into capsules. It is of no moment that the prior art recognize each and every attribute of the instant invention, merely that the prior art recognize a similar dosage formulation processed in a synonymous manner, is sufficient. The secondary reference of Arwidsson was relied upon for the sole teaching of the obviousness of filling particles,

or beads or granules into capsule form to obtain multi-particulate filled capsules. Arwidsson clearly demonstrates this teaching of filling beads into capsules, sachets or the like and additionally demonstrates the multiple unit aspect. There is no significant difference between the prior art and the instant invention since the combination of active-compounds with hydrophilic polymers is clearly exhibited by both Jenkins references and Arwidsson. Hence the instant invention is rendered obvious and unpatentable over the prior art.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Humera N. Sheikh whose telephone number is (703) 308-4429. The examiner can normally be reached on Monday through Friday from 7:00A.M. to 4:30P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page, can be reached on (703) 308-2927. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

hns

August 18, 2003

THURMAN K. PAGE
SUPERVISORY PATENT EXAMINER
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